REMARKS

Claim Amendments

Claims 9 and 11 have been amended to recite that the recited reaction results in formation of a phosphite. Claims 9 and 11 have further been amended to include the steps of removing protecting groups and oxidizing the phosphite to a phosphate, where the removing and oxidizing result in formation a negatively-charged phosphate group. Support for the amendment can, for example, be found at column 12, line 59 through column 13, line 26 of U.S. Patent No. 5,550,215, a copy of which is attached as Exhibit A. U.S. Patent No. 5,550,215 is incorporated by reference for all purposes in the instant specification at page 9, lines 11-12. No new matter has been added.

Rejection of Claims 1-3, 6, 7, 9, 12, 43 and 44 Under 35 U.S.C. § 112, Second Paragraph

Claims 1-3, 6, 7, 9, 12, 43 and 44 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner states that neither the claims nor the specification addresses the step of conversion of phosphites into phosphates. The Examiner further states that instant claims recite only the addition of a phosphoramidite as a terminal group to an unprotected nucleotide.

Contrary to the Examiner's assertions, disclosure regarding the use of phosphoramidites to produce phosphate groups is present in the instant specification, for example, through documents incorporated by reference. For example, the instant specification, at page 9, lines 11-12, incorporates by reference U.S. Patent No. 5,550,215 for all purposes. U.S. Patent No. 5,550,215, at column 12, line 59 through column 13, line 26, discusses conventional oligonucleotide synthesis from phosphoramidites. The synthesis includes removal of protecting groups (e.g., with base or thiophenol) and oxidation of phosphite to phosphate (e.g., with iodine). Claim 9 has been amended to recite removal of protecting groups and oxidation of phosphite to phosphate. Thus, it is believed that the Examiner's rejection is overcome by the instant amendment. Reconsideration and withdrawal of the rejection are respectfully requested.

In the event that the Examiner believes that the amendment to claim 9 does not overcome the rejection, Applicants request that the Examiner provide a basis for the rejection of claims 1-3, 6, 7, 12, 43 and 44. The rejection explicitly relies on the recitation of "phosphoramidite" in the claims; however, none of claims 1-3, 6, 7, 12, 43 and 44 recites phosphoramidite. Applicants thank the Examiner for clarification of this point.

Rejection of Claims 1-3, 6, 7, 9, 12, 43 and 44 Under 35 U.S.C. § 112, First Paragraph

Claims 1-3, 6, 7, 9, 12, 43 and 44 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly based on a specification that is not enabling. There are two aspects of the rejection, which are addressed separately below.

In the first aspect, the Examiner states that there is no showing of how to deliver a negatively charged phosphate group by interacting an active site with a phosphoramidite of Formula II. As discussed above, the instant specification incorporates by reference other documents that describe conventional phosphoramidite chemistry in greater detail. In particular, U.S. Patent No. 5,550,215, at column 12, line 59 through column 13, line 26, discusses conventional nucleotide synthesis from phosphoramidites, which is analogous to the claimed method (i.e., nucleotide synthesis results in the attachment of a negatively charged phosphate group). The synthesis includes removal of protecting groups (e.g., with base, thiophenol) and oxidation of phosphite to phosphate (e.g., with iodine). Thus, the instant specification is adequately enabling based on the disclosure therein and disclosure incorporated by reference. Claim 9 has been amended to recite these steps. Moreover, Applicants maintain that phosphoramidite chemistry is well-known (as evidenced by Exhibit A enclosed with the Amendment filed April 29, 2005), such that it is not necessary for the instant specification or claims to include a description of using a phosphoramidite to form a phosphate; recitation of the key reagent and end product are sufficient. Information which is well known in the art need not be described in detail in the specification. MPEP § 2163.

In the second aspect, the Examiner states that the specification does not provide support for the claimed effect of reducing non-specific binding by introducing negatively charged phosphate groups.

In the Response to Arguments, it is clear that several arguments made by Applicants in the Amendment of April 29, 2005 were misunderstood. Applicants will elaborate upon the previous remarks here. First, the Examiner appears to suggest that the interaction of molecules *in vitro* differs from that *in vivo*. While the milieu in which the molecules exist may differ, Applicants request that the Examiner provide evidence for the assertion that *in vitro* and *in vivo* interactions differ in a significant manner. Second, there is a fundamental misunderstanding of the argument involving negative charges. *In vivo*, nucleic acids exist as an essentially infinite string of negative point charges. Clearly, proper functioning of a biological system depends upon specificity of interactions between nucleic acids and other molecules. The presence of additional negative charges beyond a particular binding sequence must not disrupt this specificity of interaction. In contrast to the *in vivo* situation, nucleic acids in the claimed system exist as oligonucleotide arrays on a solid support. The oligonucleotide arrays are a decidedly finite set of negative charges. The synthesis of the oligonucleotide arrays involves the use of protecting groups, which if not removed at the end of synthesis, can react with common deprotecting agents (e.g., EDA) to form positively charged moieties (see page 12, lines 13-20 of the specification). These protecting groups and positively charged moieties are not found in an *in vivo* system. Thus, removal of protecting groups and replacement with negatively charged phosphate groups makes the oligonucleotide arrays more like the nucleic acids found *in vivo*. It should therefore be understood that the non-specific binding issue, as contemplated by the invention, exists in *in vitro* systems because of the presence of protecting groups. For these reasons, the present invention has utility on the basis of reducing or eliminating the non-specific binding associated with protecting groups attached to or adjacent to oligonucleotides in the *in vitro* system. In other words, the present invention is used to make an oligonucleotide array more closely resemble nucleic acids *in vivo*, where non-specific binding is not known to be an issue.

Applicants further note that the Examiner has not addressed the previous argument regarding the overall charge on an array. Prior to performing the claimed method, an array already has a strong negative charge due to the phosphate backbone of oligonucleotides. Accordingly, positively charged molecules would already be attracted to the oligonucleotide arrays. The claimed method is believed to have an insignificant effect on positively charged molecules for this reason. Instead, the elimination of positively charged or hydrophobic groups

is believed to have the dominant effect, because these groups are not part of a nucleic acid *in vivo*. Again, it is emphasized that the claimed method makes a synthetic oligonucleotide more closely resemble a nucleic acid found *in vivo*.

Moreover, Applicants point out that the instant application includes data in support of the claimed method. In Example 1, the control array includes a background where the protecting group remains attached to the support and the test array includes a background where the protecting group is replaced by a guanine nucleotide. As shown by claim 11, guanine nucleotides are a type of negatively charged phosphate residue according to the present invention (when R_1 is a nucleoside moiety). Table 1 in Example 1 indicates that the background fluorescence intensity, which is due largely to non-specific binding, dropped from 348 to 53-61 upon replacing the protecting group with the phosphate-containing guanine nucleotide. In other words, the signal-to-noise ratio was improved six-fold or more when the protecting group on the support was replaced with a negatively charged phosphate residue. For this reason, Applicants maintain that the application as filed demonstrates that the claimed method reduces non-specific binding.

Applicants have thus demonstrated that the specification enables one skilled in the art both to replace a protecting group with a negatively charged phosphate group and to reduce non-specific binding. Reconsideration and withdrawal of the rejection are respectfully requested.

In the event that the Examiner maintains the second aspect of the rejection, Applicants request that the Examiner provide a basis for continued rejection of claims 43 and 44. Claims 43 and 44 involve reducing the non-specific binding of a nucleic acid to an oligonucleotide array. Nucleic acids typically do not include positively charged groups. Thus, the majority of the Examiner's reasoning does not apply to these claims. Applicants thank the Examiner for clarification.

CONCLUSION

In view of the above amendments and remarks, Applicants believe the pending application is in condition for allowance.

Applicants believe no additional fee is due with this response, however, if a fee is due, please charge our Deposit Account No. 18-1945, from which the undersigned is authorized to draw, under Order No. AFMX-P02-038.

Dated: February 6, 2006

Respectfully submitted,

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